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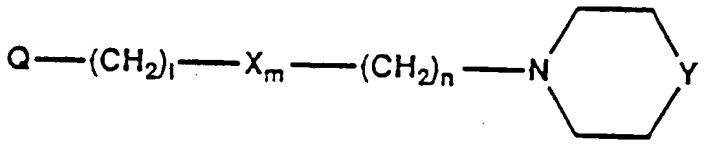
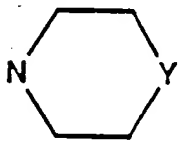
(54) Piperidine derivatives and their use as antiarrhythmic agents.

(57) A piperidine derivative of general formula (I) or a pharmaceutically acceptable salt thereof :



(I)

wherein



is any of several specified aromatic-containing groups ; X is selected from one of several hetero atom-containing groups or C_2 alkylene or a cyano-containing group ; and
Q is phenyl, cyclohexyl, piperidinyl, tetrahydropyranyl, pyridyl, pyrrolyl, N-methylpyrrolyl, thienyl, furyl, 1-hexyl, or cyano ;
from 1 to 3 hydrogen atoms in Q may be independently substituted by alkyl of from 1 to 3 carbon atoms, perfluoroalkyl of from 1 to 3 carbon atoms, acylamino of from 1 to 6 carbon atoms, perfluoroacylamino of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, alkanesulfonylamino of from 1 to 3 carbon atoms, perfluoroalkanesulfonylamino of from 1 to 3 carbon atoms, acetoxy of from 1 to 3 carbon

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atoms, aminocarbonyl, aminosulfonyl, fluoro, chloro, cyano, hydroxy, nitro, amino, imidazolylmethyl, cinnamoylamino, p-fluorobenzoyl, cyanomethyl, cyanoethyl, methoxyacetoxy, alkoxycarbonyl of from 1 to 3 carbon atoms ;
1 is an integer of from 0 to 1 ;
m is an integer of from 0 to 1 ;
n is an integer of from 0 to 6.

The derivatives are useful as antiarrhythmic agents.

Field of the Invention

The present invention relates to novel antiarrhythmic agents, more particularly to novel piperidine derivatives and their use in the treatment of arrhythmia.

Background of the Invention

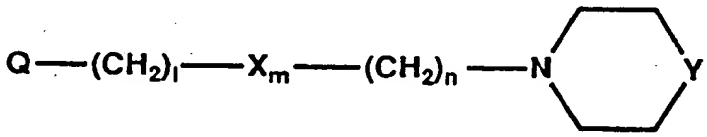
Arrhythmia is the disfunction of cardiac normal conduction, which is a life-threatening disease, because it disturbs the rhythmic beating of the heart, worsening hemodynamics. Therefore, therapy for cardiac arrhythmia is clinically essential.

Antiarrhythmic drugs have been grouped together according to the pattern of mechanism: Na channel blocker, Beta blocker, Ca channel blocker and drugs which prolong Repolarization. Drug therapy of cardiac arrhythmias is not established, because many drugs have severe adverse effects, such as undesirable hemodynamic effects, hypotension, gastrointestinal symptoms, effects on the central nervous system and arrhythmogenic effects. Also, at higher plasma concentrations of drug, cardiac toxicity may become severe, so the monitoring of plasma concentration is essential for drug therapy.

It is therefore required to develop new antiarrhythmic drugs having excellent pharmaceutical effects and safety which can be industrially prepared at low cost in a simple manner.

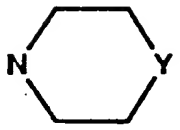
Disclosure of the Invention

It has now been found that certain piperidine derivatives have antiarrhythmic activity, which derivatives are represented by the following general fomula (I):

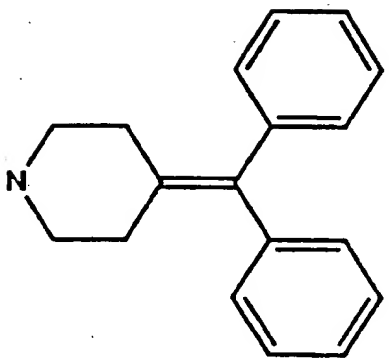


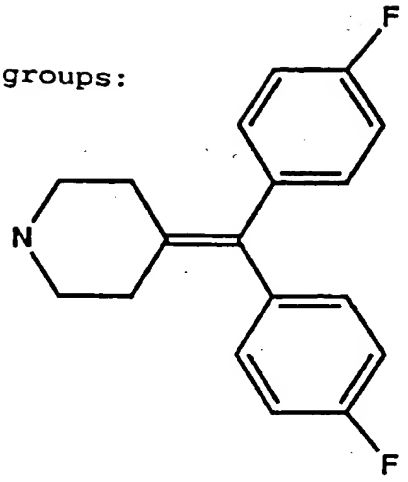
(I)

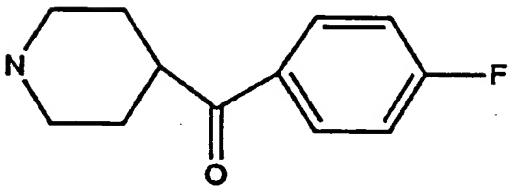
wherein

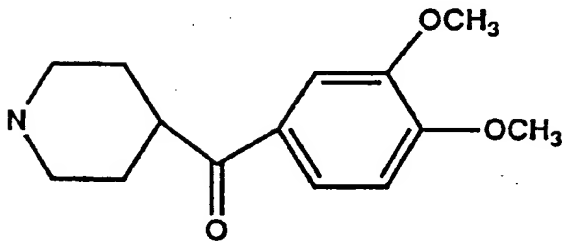


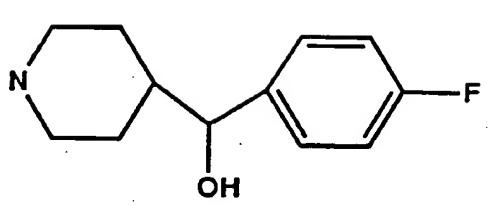
is any of the following groups:

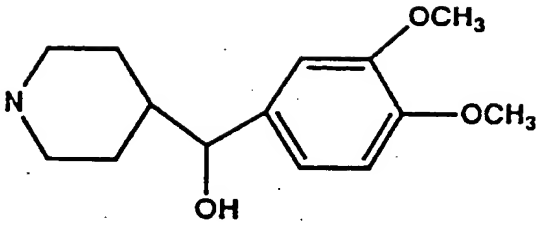












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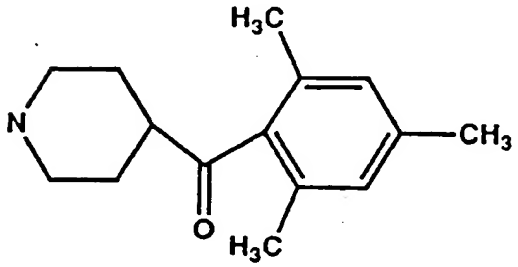

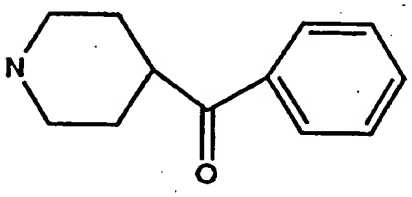

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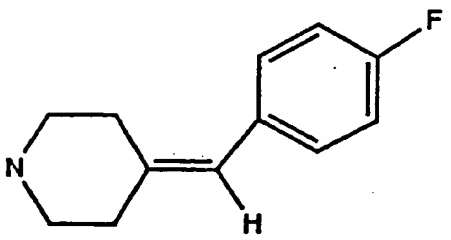

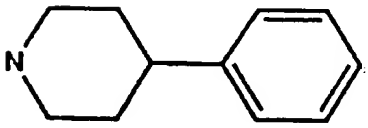

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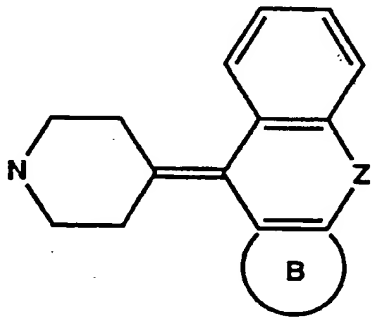
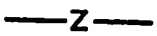


or

;

wherein B is a fused aromatic or heterocyclic ring selected from the group consisting of benzene, pyridine and thiophene;



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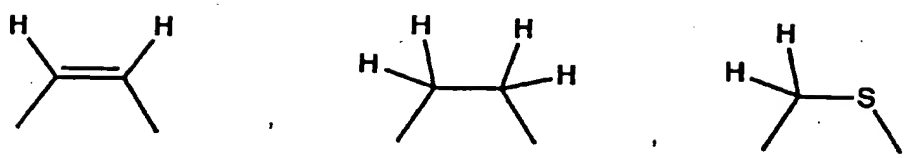

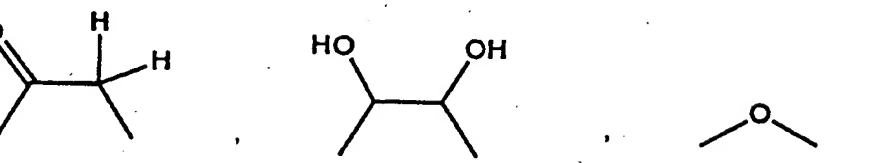

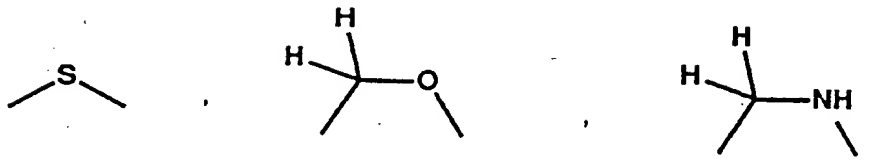

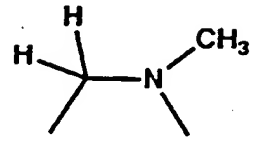

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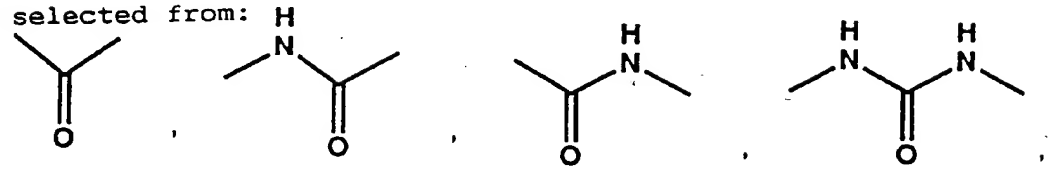
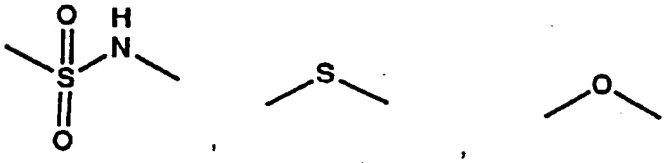
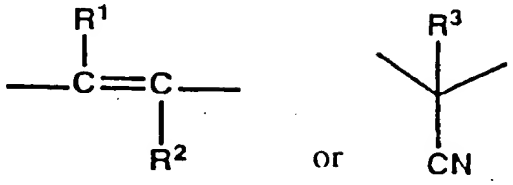


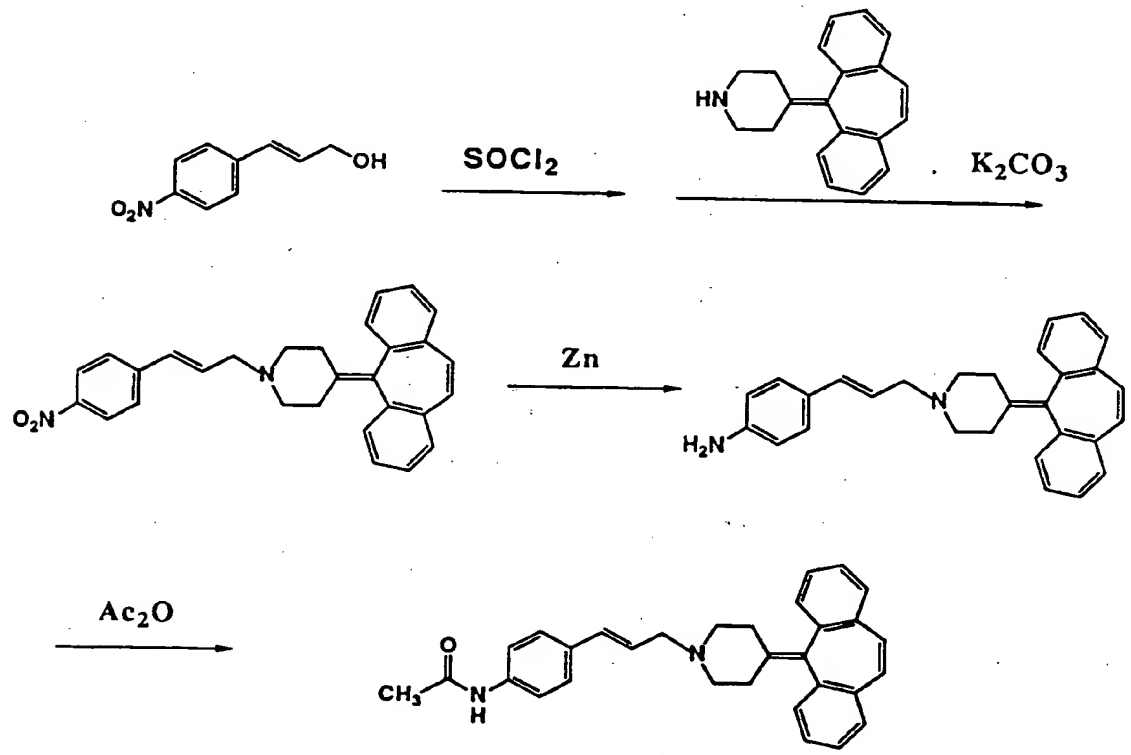




wherein R^1 and R^2 are the same or different and are independently selected from hydrogen, methyl, ethyl, or propyl; R^3 is hydrogen, alkyl of from 1 to 12 carbon atoms, or aryl of from 6 to 12 carbon atoms;
Q is phenyl, cyclohexyl, piperidinyl, tetrahydropyranyl, pyridyl, pyrrolyl, N-methylpyrrolyl, thienyl, furyl, 1-hexyl, or cyano;
from 1 to 3 hydrogen atoms in Q may be independently substituted by alkyl of from 1 to 3 carbon atoms, perfluoroalkyl of from 1 to 3 carbon atoms, acylamino of from 1 to 6 carbon atoms, perfluoroacylamino of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, alkanesulfonylamino of from 1 to 3 carbon atoms, perfluoroalkanesulfonylamino of from 1 to 3 carbon atoms, acetoxy of from 1 to 3 carbon atoms, aminocarbonyl, aminosulfonyl, fluoro, chloro, cyano, hydroxy, nitro, amino, imidazolylmethyl, cinnamoylamino, p-fluorobenzoyl, cyanomethyl, cyanoethyl, methoxyacetoxy, alkoxycarbonyl of from 1 to 3 carbon atoms;
l is an integer of from 0 to 1;
m is an integer of from 0 to 1;
n is an integer of from 0 to 6.

These compounds may be in their free base form or in the form of a pharmaceutically acceptable salt thereof.

A compound of the above formula can be prepared by the following procedure:



The pharmaceutically acceptable salts of the piperidine derivatives of this invention are acid addition salts formed from the compound and an organic or inorganic acid well known in the art as providing a pharmaceutical addition salt, such as a hydrochloride, sulfate, citrate, tartarate, mesylate, maleate, fumarate, or the like.

These salts are readily prepared by mixing a solution of equimolar amounts of the free base form of the compound and desired acid in a suitable solvent such as water, alcohol, or ether, followed by recovery of the product by collecting the precipitated salt or by evaporation of the solvent.

When used as antiarrhythmic drugs, the piperidine derivatives of the present invention may be administered by an oral or parenteral route, which may be determined depending upon age, body weight, condition of the patient. A daily dose may generally be from about 0.001 about 2000 mg/patient or animal for oral administration; in the case of patenteral administration, a daily dose may generally be from about 0.001 to about 1000 mg/patient or animal.

The piperidine derivatives of the present invention may be formulated into conventional preparation forms, for

example, tablets, powders, capsules, solutions, sugar-coated tablets or depots, which may be prepared in a conventional manner using conventional techniques. For example, tablets can be obtained by mixing a piperidine derivative of the present invention with known auxiliary substances, for example, inactive diluents (e.g. lactose, calcium carbonate or calcium phosphate), binders (e.g. gum arabic, corn starch or gelatin), sweeteners (e.g. sucrose or saccharine), flavours (e.g. peppermint, Gaultheria adenothrix oil or cherry), lubricating and wetting agents (e.g. magnesium stearate, talc or carboxymethyl cellulose).

The present invention further provides a novel antiarrhythmic agent which is a composition comprising a pharmaceutically effective amount of a piperidine derivative as defined above.

The pharmaceutical composition of the present invention is advantageous as an antiarrhythmic drug for treating mammals including humans. This can be administered perorally in the form of tablet, capsule or elixir, or parenterally in the form of a sterile solution or suspension, for the purpose of reducing or eliminating arrhythmia. The pharmaceutical composition of the present invention can be administered to patients or animals which are to be treated generally several times each in a unit dosage of from about 0.001 to about 500 mg/patient or animal, and accordingly the total dosage of the derivative may be from about 0.001 to about 2000 mg/patient or animal/day. Of course, the amount of the dosage may be varied in accordance with the condition of the disease, the weight of the patient or animal and other factors which are considered appropriate by one skilled in the art.

The above-mentioned typical combinations may be formulated as a pharmaceutical composition in a conventional manner. For example, from about 0.2 to about 500 mg of the derivative of the present invention or a pharmaceutically acceptable salt thereof or a mixture thereof is blended together with a pharmaceutically acceptable vehicle, carrier, extender, binder, antiseptic, stabilizer, flavour and the like, in an amount as required for conventional pharmaceutical preparations.

Examples of pharmaceutical additives to be used for the preparation of tablets, capsules and the like are: binders such as tragacanth, gum arabic, corn starch or gelatin; vehicles such as fine crystalline cellulose; extenders such as corn starch, pre-gelatinised starch or alginic acid; sweeteners such as sucrose, lactose or saccharin; flavours such as peppermint, an oil from Gaulthenia adenothrix Maxim or cherry. When the preparation is in the form of a capsule, this may further contain a liquid carrier such as a fat and oil, in addition to the above mentioned materials. Other various materials can further be employed so as to form coated pills or to vary the physical form of the preparation by a different method. For example, tablets can be coated with shellac, sugar or both. A syrup or elixir can contain the active compound together with sucrose as a sweetener, methyl- or propyl-paraben as an antiseptic, a dye, and cherry or orange essence as a flavour.

A sterile composition for injection can be prepared in a conventional manner, for example, by dissolving or suspending the active substance in a vehicle such as distilled water for injection, together with a natural vegetable oil such as sesame oil, coconut oil, peanut oil, cotton seed oil, or a synthetic fat vehicle such as ethyl oleate. If desired, a buffer, an antiseptic, an antioxidant or the like can be incorporated into the composition.

The present invention will be further illustrated by reference to the following examples.

PREPARATION OF COMPOUNDS

Retention factor (Rf) was determined by silica gel thin layer chromatography (TLC:Merck Art 5715). Unless otherwise noted, mass spectroscopy was determined on JEOL-DX 300 by FD mode; ^{1}H NMR spectra were obtain in $CDCl_3$ with tetramethylsilane as internal standard on a Varian VXR-300 spectrometer.
"Intermediate (1)" represents 4-(5H-dibenzo[a, d]cyclohepten-5-ylidene)piperidine.

compound 1

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-[4-(N-imidazolylmethyl)cinnamyl]piperidine
To a solution of 4-(N-imidazolylmethyl)cinnamic alcohol (4.5mmol) in CHCl3,thionyl chloride (5.4mmol) was added, and stirred for 2h at room temperature. After a usual procedure, the product was used without further purification.
The product obtained according to above-mentioned procedure was dissolved in methyl isobutyl ketone, and then intermediate (1) (4.0mmol),potassium carbonate(8.75mmol)and NaI(8.75mmol) were added to the solution,stirred at 90 °C for overnight . The mixture was washed with water,extracted with CH2Cl2, washed with 1 M HCl, saturated aqueous solution of NaHCO3, and then brine, dried over MgSO4. The solvent was evaporated at reduced pressure,the resulting mixture was purified by column chromatography (SiO2).

MS	469(M+)
NMR	
2.2-2.4(4H,m)	2.5-2.6(2H,m)
2.8-2.9(2H,m)	3.28(2H,d)
5.07(2H,s)	6.38(1H,dt)
6.52(1H,d)	6.95(2H,s)
7.0-7.6(15H,m)	

compound 2

1-[4-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butanoyl]-4-hydroxypiperidine

TLC($CHCl_3$: MeOH=9:1)	Rf=0.58
MS	442(M+)
NMR	
1.4-1.6(2H,m)	1.8-2.0(4H,m)
2.1-2.2(4H,m)	2.3-2.4(4H,m)
2.5-2.6(2H,m)	2.89(1H,m)
3.19(1H,m)	3.7-3.8(2H,m)
3.9-4.0(2H,m)	4.0-4.2(2H,m)
6.91(2H,s)	7.1-7.4(8H,m)

compound 3

4-[4-Dibenzo[b,e]thiepin-11(6H)-ylidene]-1-piperidinyl]-1-cyclohexylbutane
According to the practically same procedure described in preparation of compound 1,4-bromo-1-cyclohexylbutane and 4-dibenzo[b,e]thiepine-11(6H)-ylidenepiperidine were used.

TLC($CHCl_3$:MeOH=9:1)	Rf=0.74
MS	431(M+)
NMR	
0.8-1.0(2H,m)	1.1-1.4(10H,m)
1.4-1.6(1H,m)	1.6-1.8(6H,m)
2.1-2.4(4H,m)	2.51(2H,t)
2.6-2.8(4H,m)	3.39(1H,d)
4.99(1H,s)	6.9-7.1(4H,m)
7.2-7.4(4H,m)	

compound 4

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-nitrocinnamyl)piperidine
After the stepwise addition of 4-Nitrocinnamyl alcohol(5.58mmol) to a ice-cooled solution of $SOCl_2$(10g), the mixture was stirred for a few minites. The residue obtained by general procedure was condensed with intermediate(1) (6.59mmol) in the presence of potassium carbonate.

Yield 2.02mmol(36.2%)
MS 434(M+)
NMR
2.16-2.24(4H,m) 2.31-2.42(2H,m)
2.60-2.68(2H,m) 3.18(2H,d)
6.46(1H,dt) 6.55(1H,d)
6.92(2H,s) 7.18-7.36(8H,m)
7.42-7.48(2H,m) 8.17-8.20(2H,m)

compound 5

1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine 4-(5H-Dibenzo[a,d] cyclohepten-5-ylidene)-1-(4-nitrocinnamyl)piperidine(compound 4) was reduced by zinc in acetic acid at room temperature for 4h.

Yield 84.5%
MS 404(M+)
NMR
2.20-2.42(6H,m) 2.60-3.32(4H,m)
3.40(2H,d) 6.11(1H,dt)
6.43(1H,d) 6.59-6.64(2H,s)
6.91(2H,s) 7.14-7.36(10H,m)

compound 6

1-(4-Acetylaminocinnamyl)-4-(5H-dibenzo[a,d]cyclchepten-5-ylidene)piperidine
1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) was N-acetylated by acetic anhydride using triethyl amine as base.

Yield 92.3%
MS 446(M+)
NMR
2.18(3H,s) 2.20-2.55(6H,m)
4.70(1H,bs) 6.20(1H,dt)
6.42(1H,d) 6.91(2H,s)
7.15-7.36(10H,m) 7.42-7.56(2H,m)

compound 7

3-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-1-(4-nitrophenyl)propane
a) 1-Bromo-3-(4-nitrophenyl)propane
1-Bromo-3-phenylpropane(19.7mmol) was added slowly to a solution of sulfuric acid(7.4g) and nitric acid(5.4g) at ambient temperature and stirred at 60 °C. The residue (mixture of ortho and para) was purified by column chromatography on silica gel.

Yield 63.7%
NMR
2.20(2H,quint.) 2.92(2H,t)
3.40(2H,t) 7.35(2H,d)
8.16(2H,d)

b) compound 7

This was prepared from 1-Bromo-3-(4-nitrophenyl)propane and intermediate(1).

Yield 94.6%	
MS	436(M+)
NMR	
1.84(2H,m)	2.15(4H,m)
2.30(4H,m)	2.59(2H,m)
2.70(2H,t)	6.90(2H,s)
7.2-7.4(10H,m)	8.10(2H,d)

Compound 8

1-(4-Aminophenyl)-3-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propane

3-[4-(5H-Dibennzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-1-(4-nitrophenyl)propane(compound 7) was reduced by zinc.

Yield 97.3%	
MS	406(M+)
NMR	
1.70(2H,m)	2.0-2.6(12H,m)
3.48(2H,br)	6.55(2H,d)
6.85(2H,s)	6.92(2H,d)
7.20(4H,m)	7.25(4H,m)

Compound 9

1-(4-Acetylaminophenyl)-3-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propane

This was prepared from 1-(4-Aminophenyl)-3-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propane(compound 8) and acetic anhydride.

Yield 92.9%	
MS	48(M+)
NMR	
1.6-1.8(4H,m)	2.15(3H,s)
2.0-2.2(2H,m)	2.2-2.4(4H,m)
2.55(4H,m)	7.1-7.4(12H,m)

compound 10

N-[3-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propanoyl-3,4-dimethoxyanilide

MS(FAB,m/z)	481(M+)
NMR	
2.25-2.36 (4H,m)	2.40-2.46 (2H,m)
2.52 (2H,t)	2.70 (2H,t)
2.68-2.80 (2H,m)	3.85 (3H,s)
3.88 (3H,s)	6.79 (2H,s)
6.93 (2H,s)	7.18-7.35 (8H,m)
7.52 (1H,s)	

compound 11

4-[4-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-1-butyl] tetrahydropyran

MS	413(M+)
NMR	
1.1-1.6(10H,m)	1.7-1.8(1H,m)
2.1-2.4(8H,m)	2.5-2.6(2H,m)
3.35(2H,t)	3.93(2H,d)
6.90(2H,s)	7.2-7.4(8H,m)

compound 12

1-(N-Acetyl-4-piperidinyl)-3-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl] propane

a) 3-(4-Piperidinyl)-1-propanol

1-(4-Pyridyl)-1-propine-3-ol was hydrogenated with rhodium on alumina as catalyst.

b) 1-Acetoxy-3-(N-acetyl-4-piperidinyl)propane

This was prepared from 3-(4-Piperidinyl)-1-propanol and acetic anhydride.

NMR	
1.0-1.8(9H,m)	2.04(3H,s)
2.07(3H,s)	2.51(1H,t)
3.00(1H,t)	3.78(1H,br d)
4.04(2H,t)	4.58(1H,br d)

c) 3-(N-Acetyl-4-piperidinyl)propanol

1-Acetoxy-3-(N-acetyl-4-piperidinyl)propane was saponificated by potassium carbonate.

NMR	
1.0-1.2(2H,m)	1.2-1.4(2H,m)
1.4-1.8(6H,m)	2.08(3H,s)
2.53(1H,dt)	3.02(1H,dt)
3.64(2H,t)	3.79(1H,br d)
4.58(1H,br d)	

d) 1-(N-Acetyl-4-piperidinyl)-3-bromopropane

3-(N-Acetyl-4-piperidinyl)propanol was brominated with phosphorus tribromide.

NMR
1.0-1.2(2H,m) 1.40(2H,t)
1.50(1H,m) 1.74(2H,br t)
1.78(2H,quint) 2.08(3H,s)
2.53(1H,dt) 3.02(1H,dt)
3.40(2H,t) 3.80(1H,br d)
4.59(1H,br d)

e) compound 12

Yield 77.8%
MS 440(M+)
NMR
1.0-1.2(2H,m) 1.22(2H,m)
1.4-1.6(3H,m) 1.68(2H,m)
2.05(3H,s) 2.1-2.6(11H,m)
2.96(1H,dt) 3.74(1H,br d)
4.55(1H,br d) 6.90(2H,s)
7.2-7.4(8H,m)

compound 13

5-Acetylamino-2-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]methylindan

MS 460(M+)
NMR
2.0-2.3(7H,m) 2.3-2.5(1H,m)
2.5-2.8(6H,m) 2.9-3.1(2H,m)
6.92(2H,s) 7.0-7.5(11H,m)

compound 14
4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,4-dimethoxycinnamyl)piperidine

a) 4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,4-dimethoxycinnamoyl)piperidine
2,4-Dimethoxycinnamic acid(10.0mmol) and intermediate(1) was condencedby N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride.

b) compound 14
4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,4-dimethoxycinnamoyl)piperidine was reduced with lithium alminium hydride.

Yield 12.3%
MS 449(M+)
NMR
2.13-2.23(4H,m) 2.30-2.50(2H,m)
2.62(2H,m) 3.13(2H,d)
3.78(6H,s) 6.15(1H,tt)
6.42(2H,m) 6.68(1H,d,J=15.9Hz)
6.91(2H,s) 7.18-7.35(9H,m)

compound 15

1-(4-Cyanocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

a) 4-Cyanocinnamylalcohol

A Heck reaction of 4-bromobenzonitrile and acrylic acid gave 4-cyanocinnamic acid. The acid was reduced to the corresponding alcohol with ethyl chloroformate and then sodium borohydride.

Yield 78.6%
NMR
4.38(2H,dd) 6.49(1H,m)
6.65(1H,d) 7.44(2H,d)
7.40(2H,d)

b) compound 15

MS 414(M+)
NMR
2.12-2.22(4H,m) 2.30-2.42(2H,m)
2.52(2H,m) 3.15(2H,d)
6.42(2H,m) 6.92(2H,s)
7.18-7.35(8H,m) 7.40(2H,d)
7.58(2H,d)

compound 16

1-Cyclohexy1-4-[4-(10,11-dihydroxy-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butane

A osmium tetraoxide(0.4mmol) in acetone was added to the 50% aqueous solution of acetone dissolved in 1-Cyclohexyl-4-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl)butane (4.8mmol) and N-methylmorpholine-N-oxide (7.2mmol). The mixture was stirred for over night at ambient temperature.

MS 445(M+)
0.7-1.4(11H,m) 1.4-1.8(8H,m)
2.6-3.0(8H,m) 3.05(1H,bs)
3.26(1H,bs) 5.21(2H,s)
7.0-7.6(4H,m)

compound 17

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-propanoylaminocinnamyl)piperidine1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(composed 5) was N-acylated.

Yield 43.9%
MS 460(M+)
NMR
1.22(3H,t) 2.2-2.6(8H,m)
2.7-2.9(2H,m) 3.23(2H,d)
4.79(1H,bs) 6.1-6.3(1H,m)
6.43(1H,dd) 6.93(2H,s)
7.1-7.55(12H,m)

compound 18

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-ethoxycarbonylaminocinnamyl)piperidine
This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and ethyl chloroformate.

Yield 56.7%	
MS	476(M+)
NMR	
1.30(3H,t)	2.2-2.9(8H,m)
3.26(2H,dd)	4.22(2H,q)
6.1-6.3(1H,m)	6.46(1H,d)
6.67(1H,bs)	6.93(2H,s)
7.1-7.4(12H,m)	

compound 19

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methanesulfonylaminocinnamyl)piperidine
This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and methanesulfonyl chloride.

Yield 67.0%	
MS	482(M+)
NMR	
2.1-2.5(6H,m)	2.5-2.7(2H,m)
3.17(2H,d)	3.39(3H,s)
6.2-6.4(1H,m)	6.49(1H,d)
6.93(2H,s)	7.1-7.5(12H,m)

compound 20

4-(5H-Dibenzo [a,d]cyclohepten-5-ylidene)-1-(3-methoxycarbonylcinnamyl)piperidine
According to the practical same procedure of compound 16 ,this compound was obtained.

MS	447(M+)
NMR	
2.16-2.26(4H,m)	2.30-2.44(2H,m)
2.52(2H,m)	3.14(2H,d)
3.91(3H,s)	6.38(1H,m)
6.52(1H,d)	6.92(2H,s)
7.18-7.35(9H,m)	7.52(1H,d)
7.88(1H,d)	8.01(1H,s)

compound 21

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methoxycarbonylaminocinnamyl)piperidine
This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and methyl chloroformate.

Yield 97.5%	
MS	462(M+)
NMR	
2.2-2.9(8H,m)	3.10(2H,m)
3.78(3H,s)	6.2-6.4(1H,m)
6.56(1H,d)	6.72(1H,bs)
6.92(2H,s)	7.1-7.4(12H,m)

compound 22

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-pivaloylaminocinnamyl)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and pivaloyl chloride.

Yield 92.0%	
MS	488(M+)
NMR	
1.34(9H,s)	2.2-3.2(10H,m)
6.2-6.42(1H,m)	6.55(1H,d)
6.93(2H,s)	7.1-7.44(10H,m)
7.45-7.6(2H,m)	

compound 23

4-(5H-Dibenzo[a,d]cyclohepten-5 -ylidene)-1-(4-trifluoroacetylaminocinnamyl)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and trifluoroacetic anhydride.

Yield 46.0%	
MS	500(M+)
NMR	
2.4-3.7(10H,m)	6.2-6.4(1H,m)
6.58(1H,dd)	6.93(2H,s)
7.17(2H,d)	7.2-7.45(8H,m)
7.69(2H,dd)	8.36(1H,bs)

compound 24

1-(4-Butanoylaminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

This compound was prepared from 1-(4-Aminocinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine(compound 5) and butanoic acid.

Yield 68.5%

MS	474(M+)
NMR	
0.99(3H,q)	1.6-1.8(2H,m)
2.2-2.43(6H,m)	2.44-2.7(2H,m)
2.8-3.1(2H,m)	3.35(2H,d)
5.50(1H,bs)	6.1-6.3(1H,m)
6.45(1H,dd)	6.92(2H,s)
7.1-7.4(10H,m)	7.49(2H,dd)

The following composed were prepared according to the above-mentioned procedures.

compound 25

1-(4-Ethoxycarbonylaminocinnamyl)-4-(4-fluorobenzoyl)piperidine

MS	410(M+)
NMR	
1.33(3H,t)	1.8-2.4(6H.m)
3.18(2H,m)	3.43(3H,m)
4.21(2H,m)	6.32(1H,dt)
6.58(1H,d)	6.6(1H,s)
7.1-7.4(6H,m)	7.92(2H,m)

compound 26

4-(4-Fluorobenzoyl)-1-(4-methoxycarbonylaminocinnamyl)piperidine

MS	396(M+)
NMR	
1.9-2.3(4H,m)	2.70(3H,m)
3.28(2H,m)	3.42(3H,m)
3.99(3H,m)	6.33(1H,dt)
6.58(1H,d)	6.80(1H,s)
7.1-7.5(6H,m)	7.97(2H,m)

compound 27

4-(4-Fluorobenzoyl)-1-(4-propanoylaminocinnamyl)piperidine

MS	394(M+)
NMR	
1.23(3H,t)	1.7-2.2(6H,m)
2.41(2H,q)	3.1-3.5(5H,m)
6.33(1H,dt)	6.58(1H,d)
7.0-7.5(7H,m)	7.98(2H,m)

compound 28

4-(4-Fluorobenzoyl)-1-(4-trifluoroacetylaminocinnamyl)piperidine

MS	435(M+)
NMR	
2.1-2.2(4H,m)	2.95-3.3(5H,m)
3.80(2H,m)	6.25(1H,dt)
6.68(1H,d)	7.1-7.5(7H,m)
7.98(2H,m)	

compound 29

1-(4-Acetylaminocinnamyl)-4-(4-fluorobenzoyl)piperidine

MS	380(M+)
NMR	
1.75-1.95(5H,m)	2.1-2.3(4H,m)
3.0-3.3(5H,m)	6.22(1H,dt)
6.50(1H,d)	7.05-7.55(7H,m)
7.98(2H,m)	

compound 30

1-(4-Aminocinnamyl)-4-(4-fluorobenzoyl)piperidine

MS	338(M+)
NMR	
1.8-2.2(4H,m)	2.95-3.3(5H,m)
3.68(2H,m)	6.10(1H,dt)
6.41(1H,d)	6.62(2H,m)
7.05-7.40(6H,m)	7.97(2H,m)

compound 31

4-(4-Fluorobenzoyl)-1-(4-nitrocinnamyl)piperidine

MS	368(M+)
NMR	
1.8-2.2(4H,m)	3.0-3.35(5H,m)
3.8(2H,m)	6.36(1H,dt)
6.57(1H,d)	7.05-7.5(6H,m)
7.98(2H,m)	

compound 32

1-(4-Aminocarbonylcinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.23
MS 432(M+)

compound 33

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-trifluoromethylcinnamyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.85
MS 457(M+)

compound 34

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-cyanomethylcinnamyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.89
MS 428(M+)

compound 35

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,4-dichlorocinnamyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.72
MS 457(M+)

compound 36

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,4-dimethoxy-2-nitrocinnamyl)piperidine

TLC(HEXANE:Ethyl acetate=1:1) Rf=0.13
MS 457(M+)

compound 37

4-Dibenzo[b,e]thiepin-11(6H)-ylidene-1-(4-nitrocinnamyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.89
MS 454(M+)
NMR
2.1-2.3(4H,m) 2.4-2.6(2H,m)
2.6-2.8(2H,m) 3.21(2H,d)
3.41(1H,d) 4.98(1H,d)
6.48(1H,dt) 6.61(1H,d)
7.0-7.1(4H,m) 7.2-7.4(4H,m)
7.4-7.5(2H,m) 8.1-8.2(2H,m)

compound 38

1-(4-Aminocinnamyl)-4-dibenzo[b,e]thiepin-11(6H)-ylidenepiperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.65
MS	424(M+)
NMR	
2.1-2.8(8H,m)	3.13(2H,d)
3.39(1H,d)	3.68(2H,bs)
4.95(1H,d)	6.08(1H,dt)
6.39(1H,d)	6.5-6.6(2H,m)
7.0-7.1(5H,m)	7.1-7.3(5H,m)

compound 39

1 -(4-Acethylaminocinnamyl)-4-dibenzo[b,e]thiepin-11(6H)-ylidenepiperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.58
MS	466(M+)
NMR	
2.15(3H,s)	2.2-2.9(8H,m)
3.22(2H,d)	3.40(1H,d)
4.91(1H,d)	6.21(1H,dt)
6.48(1H,d)	7.0-7.5(13H,m)

compound 40

4-(5H-Dibenzo[a,d]-cyclohepten-5-ylidene)-1-(2,5-dimethoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.73
MS	449(M+)
NMR	
2.05-2.23(4H,m)	2.30-2.45(2H,m)
2.50-2.66(2H,m)	3.15(2H,d)
3.75(6H,s)	6.15(1H,m)
6.45-7.00(4H,m)	6.91(2H,s)
7.18-7.35(8H,m)	

compound 41

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,3-dimethoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.90
MS	449(M+)
NMR	
2.1-2.2(4H,m)	2.3-2.4(2H,m)
2.5-2.7(2H,m)	3.13(2H,d)
3.77(3H,s)	3.80(3H,s)
6.28(1H,dt)	6.79(1H,d)
6.90(2H,s)	7.0-7.1(2H,m)
7.2-7.4(9H,m)	

compound 42

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,5-dimethoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.73
MS	449(M+)
NMR	
2.05-2.23(4H,m)	2.28-2.42(2H,m)
2.50-2.66(2H,m)	3.10(2H,d)
3.78(6H,s)	6.10-6.42(3H,m)
6.52(2H,m)	6.91(2H,s)
7.18-7.35(8H,m)	

compound 43

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-methoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.87
MS	419(M+)
NMR	
2.2-2.3(4H,m)	2.3-2.4(2H,m)
2.6-2.7(2H,m)	3.15(2H,d)
3.79(3H,s)	6.28(1H,dt)
6.80(1H,d)	6.8-6.9(1H,m)
6.92(2H,s)	7.1-7.4(11H,m)

compound 44

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3-methoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.89
MS	419(M+)
NMR	
2.1-2.2(4H,m)	2.2-2.4(2H,m)
2.5-2.7(2H,m)	3.12(2H,d)
3.78(3H,s)	6.23(1H,dt)
6.42(1H,d)	6.7-6.9(4H,m)
6.92(2H,s)	7.2-7.4(8H,m)

compound 45

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.85
MS	419(M+)
NMR	
2.1-2.2(4H,m)	2.3-2.4(2H,m)
2.6-2.7(2H,m)	3.12(2H,d)
3.79(3H,s)	6.12(1H,dt)
6.41(1H,d)	6.83(2H,d)
6.91(2H,s)	7.1-7.3(10H,m)

compound 46

4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-nitrocinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.93
MS	436(M+)
NMR	
2.7-3.0(8H,m)	3.3-3.4(4H,m)
3.75(2H,d)	6.7-6.8(2H,m)
7.0-7.2(8H,m)	7.5-7.6(2H,m)
8.1-8.2(2H,m)	

compound 47

1-(4-Aminocinnamyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.64
MS	405(M+)
NMR	
2.4-2.5(4H,m)	2.6-2.7(2H,m)
2.81(2H,dt)	3.12(2H,d)
3.3-3.4(2H,dt)	3.67(2H,bs)
6.08(1H,dt)	6.39(1H,d)
6.60(2H,d)	7.0-7.2(10.m)

compound 48

1-(4-Acethylaminocinnamyl)4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.54
MS	448(M+)
NMR	
2.4-2.6(4H,m)	2.7-2.8(8H,m)
3.21(2H,d)	6.21(1H,dt)
6.44(1H,d)	7.0-7.2(8H,m)
7.34(2H,d)	7.44(2H,d)

compound 49

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-fluorocinnamyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.88
MS 445(M+)
NMR
2.1-2.2(4H,m) 2.3-2.4(2H,m)
2.6-2.8(2H,m) 3.09(2H,d)
6.17(1H,dt) 6.42(1H,d)
6.87(2H,s) 6.9-7.0(2H,m)
7.2-7.3(10H,m)

compound 50

3-[4-(5H-Dibenzo [a,d]cyclohepten-5-ylidene)-1-piperidinyl]-1-(3-pyridyl)-1-propene

TLC(CHCl3:MeOH 9:1) Rf=0.44
MS 390(M+)
NMR
2.1-2.2(4H,m) 2.3-2.5(2H,m)
2.55-2.65(2H,m) 3.09(2H,d)
6.31(1H,dt) 6.43(1H,d)
6.90(2H,s) 7.1-7.3(9H,m)
7.62(1H,d) 8.41(1H,dd)
8.54(1H,d)

compuond 51

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-hydroxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.55
MS(FAB.m/z) 406(MH+)
NMR
2.1-2.3(4H,m) 2.3-2.5(2H,m)
2.6-2.8(2H,m) 3.07(2H,d)
5.97(1H,dt) 6.37(1H,d)
6.63(2H,d) 6.87(2H,s)
7.0-7.3(11H,m)

compound 52

1-(4-Acetoxycinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH= 9:1) Rf=0.87
MS 447(M+)
NMR
2.1-2.2(4H,m)2.29(3H,s)
2.3-2.4(2H,m) 2.6-2.7(2H,m)
3.12(2H,d) 6.21(1H,dt)

6.43(1H,d) 6.92(2H,s)
6.9-7.0(2H,m) 7.2-7.4(10H,m)

compound 53

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-hydroxy-3-methoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.87
MS 435(M+)
NMR
2.1-2.2(4H,m) 2.3-2.4(2H,m)
2.6-2.7(2H,m) 3.08(2H,d)
3.81(3H,s) 6.09(1H,dt)
6.39(1H,d) 6.78(1H,s)
6.8-6.9(2H,m) 6.87(2H,s)
7.1-7.3(9H,m)

compound 54

1-(4-Acetoxy-3-methoxycinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.83
MS 477(M+)
NMR
2.1-2.2(4H,m) 2.29(3H,s)
2.3-2.4(2H,m) 2.6-2.7(2H,m)
3.09(2H,d) 3.81(3H,s)
6.08(1H,dt) 6.38(1H,d)
6.80(2H,s) 6.9-7.4(11H,m)
7.2-7.4(9H,m)

compound 55

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3-hydroxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.45
MS 405(M+)
NMR(CD3OD)
2.10-2.30(4H,m) 2.31-2.50(2H,m)
2.70(2H,m) 3.16(2H,d)
6.42(1H,m) 6.70(1H,m)
6.84-6.95(2H,m) 6.95(2H,s)
7.10-7.38(10H,m)

compound 56

1-(3-Acetoxycinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.80
MS	447(M+)
NMR	
2.13-2.24(4H,m)	2.30-2.45(2H,m)
2.62(2H,m)	3.14(2H,d)
6.28(1H,m)	6.43(1H,d)
6.92(2H,s)	6.92-6.97(1H,m)
7.04(1H,s)	7.18-7.35(10H,m)

compound 57

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-[3-(2-methoxyacethoxy)cinnamyl] piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.65
MS	477(M+)
NMR(hydrochloride)	
2.21-2.40(2H,m)	2.48-2.60(4H,m)
2.92-3.15(2H,m)	3.20-3.65(2H,m)
3.54(3H,s)	4.26(2H,s)
6.40-6.60(2H,m)	6.92(2H,s)
7.00-7.39(12H,m)	

compound 58

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-methoxycarbonylcinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.55
MS	447(M+)
NMR	
2.52-2.68(4H,m)	2.92-3.10(2H,m)
3.30-3.50(2H,m)	3.62(2H,d)
6.42(1H,dt)	6.91(2H,s)
7.18(1H,d)	7.24-7.40(8H,m)
7.42-7.60(3H,m)	7.90-7.95(1H,m)

compound 59

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methoxycarbonylcinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.50
MS	447(M+)
NMR	
2.15-2.24(4H,m)	2.32-2.45(2H,m)
2.60-2.68(2H,m)	3.16(2H,d)
3.90(3H,s)	6.39(1H,dt)
6.50(1H,d)	6.92(2H,s)
7.20-7.36(8H,m)	7.37-7.41(2H,m)
7.96-8.00(1H,m)	

compound 60

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3-methoxy-2-nitrocinnamyl)piperidine

TLC(HEXANE:EtO \c=1:1)	Rf=0.30
MS	464(M+)
NMR	
2.1-2.23(3H,m)	2.24-2.42(2H,m)
2.43-2.7(3H,m)	3.07(2H,d)
3.81(3H,s)	6.37(2H,s)
6.8-7.0(3H,m)	7.05-7.4(10H,m)

compound 61

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-ethoxycarboxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.83
MS	477(M+)
NMR	
1.23(3H,t)	2.1-2.2(4H,m)
2.3-2.4(2H,m)	2.5-2.7(2H,m)
3.13(2H,d)	4.18(2H,q)
6.24(1H,d)	6.43(1H,d)
6.90(2H,s)	7.0-7.1(2H,m)
7.1-7.4(10H,m)	

compound 62

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-methoxyacethoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.75
MS	477(M+)
NMR	
2.0-2.2(4H,m)	2.4-2.6(2H,m)
2.5-2.7(2H,m)	3.17(2H,d)
3.52(3H,s)	4.24(2H,s)
6.22(1H,dt)	6.44(1H,d)
6.95(2H,s)	7.0-7.4(12H,m)

compound 63

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,4-dihydroxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.35
MS(FAB.m/z)	422(M+)
NMR	
2.0-2.3(4H,m)	2.4-2.6(2H,m)
2.6-2.8(2H,m)	3.17(2H,dt)
6.27(1H,dt)	6.41(1H,d)
6.87(2H ,s)	6.9-7.5(13H,m)

compound 64

4-Dibenzo[b,e]thiepin-11(6H)-ylidene-1-(2,4-dimethoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.75
MS	469(M+)

compound 65

4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,4-dimethoxycinnamyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.71
MS	451(M+)

compound 66

1-(4-Aminosulfonylcinnamyl)-4-dibenzo[b,e]oxepin-11(6H)-ylidenepiperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.32
MS	475(M+)

compound 67

1-(4-Aminosulfonylcinnamyl)-4-(9-thioxanthylidene)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.35
MS	475(M+)

compound 68

1-(4-Aminosulfonylcinnamyl)-4-(9-xanthylidene)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.31
MS	458 (M+)

compound 69

1-(4-Aminosulfonylcinnamyl)-4-diphenylmethylenepiperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.31
MS	444(M+)

compound 70

1-(4-Aminosulfonylcinnamyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.34
MS	471(M+)

compound 71

1-(4-Aminosulfonyl-α-methylcinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.29
MS	483(MH+)

compound 72

1-(4-Aminosulfonyl-β-methylcinnamyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.45
MS	483(MH+)

compound 73

1-(2-Chlorobenzyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

MS	397(M+)
H-NMR	
2.1-2.8(8H,m)	3.63(2H,bs)
6.90(2H,s)	7.1-7.3(12H,m)

compound 74

1-Cyclohexyl-3-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]propane

MS	397(M+)
H-NMR	
0.8-2.1(15H,m)	2.47(2H,dd)
2.68(2H,d)	2.7-2.9(2H,m)
3.0(2H,dd)	3.49(2H,d)
6.94(2H,s)	7.1-7.4(8H,m)

compound 75

1-Cyclohexyl-4-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butane

MS	411(M+)
H-NMR	
0.8-2.1(15H.m)	2.47(2H.dd)
2.68(2H,d)	2.7-2.9(2H,m)
3.0(2H.dd)	3.49(2H,d)
6.92(2H,s)	7.1-7.4(8H,m)

compound 76

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-hexylpiperidine

Yield 95.6%	
TLC(CHCl3: MeOH=9:1)	Rf=0.68
MS	357(M+)
H-NMR(CDCL3)	
0.85(3H,d,J=8Hz)	1.2-1.4(6H,m)
1.7-1.9(2H,m)	2.31(2H,dd,J=12,8Hz)
2.53(2H.d,J=12Hz)	2.7-2.8(2H.m)
3.14(2H,td.J=8,3Hz)	3.40(2H,d,J=12Hz)
6.92(2H,s)	7.2-7.4(8H,m)

compound 77

1-Decyl-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

Yield 66.7%	
TLC(CHCl3:MeOH=9:1)	Rf=0.75
MS	413(M+)

NMR(hydrochloride)	
0.85(3H,t,J=8Hz)	1.2-1.4(14H,m)
1.7-1.9(2H,m)	2.33(2H,dd,J=12,8Hz)
2.54(2H,d,J=12Hz)	2.7-2.8(2H,m)
3.15(2H,td,J=8,3Hz)	3.39(2H,d,J=12Hz)
6.92(2H,s)	7.1-7.4(8H,m)

compound 78

5-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-2-(3,4-dichlorophenyl-2-isopropylvaleronitrile

Yield 69.1%
TLC(CHCl3: MeOH=9:1) Rf=0.60
MS 542(M+)
H-NMR(CDCL3)
0.77(3H,d,J=8Hz) 1.18(3H,d,J=8Hz)
2.0-3.4(15H,m) 6.90(2H,s)
7.18(H,dd,J=9,2Hz) 7.2-7.4(8H,m)
7.48(1H,d,J=9Hz) 7.53(1H,s)

compound 79

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-[3-[2-(cinnamoylamino)phenylthio]-1-propyl)piperidine

TLC(CHCl3:MeOH=9:1) Rf=0.66
MS 568(M+)
H-NMR(CDCL3)
1.73(2H,tt,J=7,7Hz) 2.0-2.2(4H,m)
2.3-2.4(2H,m) 2.38(2H,t,J=7Hz)
2.5-2.6(2H,m) 2.78(2H,t,J=7Hz)
6.59(1H,d,J=16Hz) 6.88(2H,s)
7.08(1H,tt,J=8,1Hz) 7.1-7.4(12H,m)
7.5-7.6(3H,m) 7.76(1H,d,J=16Hz)
8.55(1H,d,J=8Hz) 8.78(1H,bs,NH)

compound 80

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-cinnamylpiperidine

TLC(CHCl3: MeOH=9:1) Rf=0.69
MS 389(M+)
H-NMR(CDCL3)
2.1-2.3(4H,m) 2.4-2.5(2H,m)
2.6-2.7(2H,m) 3.14(2H,d,J=7Hz)
6.26(2H,dt,J=16,7Hz) 6.48(2H,d,J=16Hz)
6.92(2H,s) 7.1-7.4(8H,m)

compound 81

5-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-2,2-diphenylvaleronitrile

Yield 57.7%
TLC(CHCl3: MeOH=9:1) Rf=0.74
MS 506(M+)
H-NMR(CDCL3)
1.5-1.7(2H,m) 2.0-2.2(4H,m)
2.3-2.6(8H,m) 6.87(2H,s)
7.1-7.4(18H,m)

compound 82

5-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-2-(3-trifluoromethylphenyl)-2-isopropylvaleronitrile

Yield 47.5%	
TLC(CHCl3: MeOH=9:1)	Rf=0.75
MS	540(M+)
H-NMR(CDCL3)	
0.76(3H,d,J=7Hz)	1.0-1.2(1H,m)
1.5-1.6(1H,m)	1.9-2.5(13H,m)
6.88(2H,s)	7.1-7.3(8H,m)
7.48(1H,d,J=8Hz)	7.56(1H,d,J=8Hz)
7.59(1H,s)	

compound 83

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2-fluorobenzyl)piperidine

TLC(CHCl3: MeOH=9:1)	Rf=0.75
MS	381(M+)
H-NMR(CDCL3)	
2.1-2.2(4H,m)	2.3-2.4(2H,m)
2.5-2.6(2H,m)	3.53(2H,s)
6.88(2H,s)	6.96(1H,dd,J=8,8Hz)
7.04(1H,dd,J=7,7Hz)	7.1-7.4(10H,m)

compound 84

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(4-fluorophenylethyl)piperidine

TLC(CHCl3: MeOH=9:1)	Rf=0.55
MS	395(M+)
H-NMR(CDCL3)	
2.1-2.8(12H,m)	6.9-7.4(2H,m)

compound 85

5-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-2-(3-trifluoromethylphenyl)valeronitrile

TLC(CHCl3: MeOH=9:1)	Rf=0.56
MS	498(M+)
H-NMR(CDCL3)	
1.5-2.7(14H,m)	3.97(1H,t,J=7Hz)
6.90(2H,s)	7.1-7.6(12H,m)

compound 86

1-(3-Aminobenzyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

TLC(CHCl3: MeOH=9:1)	Rf=0.62
MS	378(M+)
H-NMR(CDCL3)	
2.1-2.8(8H,m)	3.50(2H,s)
3.4-3.8(2H,bs)	6.5-6.8(2H,m)
6.93(2H,s)	7.0-7.4(10H,m)

compound 87

4-[4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]-3',4'-dimethoxybutyrophenone

TLC(CHCl3: MeOH=9:1)	Rf=0.52
MS	479(M+)
H-NMR(CDCL3)	
1.8-2.6(12H,m)	2.95(2H,t,J=8Hz)
3.93(3H,s)	3.96(3H,s)
6.85(1H,d,J=10Hz)	6.88(2H,s)
7.2-7.4(8H,m)	7.5-7.7(2H,m)

compound 88

1-(4-Cyanobenzyl)-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.70
MS(FD.m/z)	388(M+)
H-NMR	
2.2-2.5(2H,m)	2.5-2.8(2H,m)
3.0-3.4(4H,m)	4.03(2H,d)
6.92(2H,s)	7.1-8.0(12H,m)

compound 89

1-Cyclohexyl-4-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]butane

TLC(HEXANE.:EtOAc=1:1)	Rf=0.67
MS	413(M+)
H-NMR	
0.80-0.88(2H,m)	1.10-1.73(15H,m)
2.12-2.19(2H,m)	2.28-2.30(2H,m)
2.32-2.47(4H,m)	2.64-2.69(2H,m)
2.77-2.86(2H,m)	3.36-3.45(2H,m)
7.05-7.15(8H,m)	

compound 90

Cyclohexyl-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]methane

TLC(CHCl3:MeOH=9:1)	Rf=0.58

MS(FD.m/z)	369(M+)
H-NMR	
0.7-2.9(20H,m)	6.91(2H,s)
7.05-7.4(8H,m)	

compound 91

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(2,3-dimethoxybenzyl)piperidine

TLC(CHCl3:MeOH=9:1)	Rf=0.63
MS(FD.m/z)	423(M+)
H-NMR	
2.0-2.8(10H,m)	3.80(3H,s)
3.84(3H,s)	6.7-7.4(11H,m)
6.89(2H,s)	

compound 92

3-Cyanopropyl-4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine

NMR	
1.62-2.72(14H,m)	6.92(2H,s)
7.10-7.30(8H,m)	

compound 93

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-(3,4-dimethoxyphenacyl)piperidine

MS	451(M+)
NMR	
2.15-2.30(4H,m)	2.37-2.45(2H,m)
2.65-2.75(2H,m)	3.70(2H,s)
3.90(3H,s)	3.92(3H,s)
6.85(1H,d)	6.90(2H,s)
7.18-7.34(8H,m)	7.59(1H,d)
7.66(1H,dd)	

compound 94

1-Cyclohexyl-6-[4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-piperidinyl]hexane

TLC(CHCl3:MeOH=9:1)	Rf=0.65
MS(FD.m/z)	439(M+)
H-NMR	
0.8-1.0(2H,m)	1.1-1.4(10H,m)
1.5-1.7(8H,m)	2.2-2.4(1H,m)
2.5-2.9(5H,m)	3.0-3.2(2H,m)
3.4-3.6(3H,m)	6.92(2H,s)
7.1-7.4(8H,m)	

compound 95

1-(4-Cyclohexylbutyl)-4-(9-thioxanthylidene)piperidine

TLC(CHCl3: MeOH=9:1)	Rf=0.69
MS(FD.m/z)	417(M+)
H-NMR	
0.8-1.0(2H,m)	1.1-1.4(9H,m)
1.5-1.7(6H,m)	2.2-2.4(2H,m)
2.5-2.6(2H,m)	2.8-2.9(2H,m)
2.9-3.1(6H,m)	7.1-7.5(8H,m)

compound 96

1-(4-Cyclohexylbutyl)4-(9-xanthylidene)piperidine

TLC(CHCl3: MeOH=9:1)	Rf=0.74
H-NMR	
0.8-1.0(2H,m)	1.1-1.4(9H,m)
1.5-1.7(6H,m)	2.3-2.4(2H,m)
2.52(4H,t)	2.91(4H,t)
7.0-7.4(8H,m)	

compound 97

5-[4-(4-Fluorobenzoyl)-1-piperidinyl]-2-isopropyl-2-(3,4,5-trimethoxyphenyl)valeronitrile

TLC(CHCl3: MeOH=9:1)	Rf=0.56
MS	497(M+)
H-NMR(CDCL3)	
0.76(3H,bs)	1.0-1.2(1H,m)
1.16(3H,bs)	1.4-2.5(12H,m)
2.9-3.4(3H,m)	3.82(3H,s)
3.87(3H,s)	6.6-6.8(2H,m)
6.6-6.8(2H,m)	7.0-7.2(2H,m)
7.8-8.1(2H,m)	

compound 98

2-(3,4-Dimethoxyphenyl)-2-dodecyl-5-[4-(4-fluorobenzoyl)-1-piperidinyl]valeronitrile

TLC(CHCl3: MeOH=9:1) Rf=0.70
MS 592(M+)
H-NMR(DMSO-d6)
0.84(3H,t,J=8Hz) 1.2-1.5(22H,m)
1.8-2.1(8H,m) 2.9-3.1(4H,m)
3.4-3.5(2H,m) 3.6-3.8(1H,m)
3.76(3H,s) 3.79(3H,s)
6.9-7.0(3H,m) 7.40(2H,dd,J=8,8Hz)
8.07(2H,dd,J=10,8Hz)

compound 99

5-[4-(3,4-Dimethoxybenzoyl)-1-piperidinyl]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile

TLC(CHCl3: MeOH=9:1) Rf=0.83
MS 508(M+)
H-NMR(CDCL3)
0.80(3H,t,J=6Hz) 1.21(3H,t,J=6Hz)
2.0-3.8(16H,m) 3.89(3H,s)
3.93(3H,s) 3.96(6H,s)
6.86(1H,d,J=8Hz) 6.91(1H,d,J=8Hz)
6.94(1H,d,J=2Hz) 7.00(1H,dd,J=8,2Hz)
7.44(1H,d,J=2Hz) 7.49(1H,dd,J=8,2Hz)

compound 100

5-{4-[Bis(4-fluorophenyl)methylene]-1-piperidinyl}-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile

TLC(CHCl3: MeOH=9:1) Rf=0.54
MS 544(M+)
H-NMR(CDCL3)
0.78(3H,d,J=8Hz) 1.20(3H,d,J=8Hz)
1.6-3.6(15H,m) 3.87(3H,s)
3.94(3H,s) 6.8-7.1(11H,m)

compound 101

2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[4-(2,4,6-trimethylbenzoyl)-1-piperidinyl]valeronitrile

TLC(CHCl3: MeOH=9:1) Rf=0.64
MS 490(M+)
H-NMR(CDCL3)
0.8-1.3(6H,m) 1.9-3.6(25H,m)
3.9-4.0(6H,m) 6.8-7.0(5H,m)

compound 102

2-(3,4-Dimethoxyphenyl)-5-[4-(4-fluorobenzoyl)-1-piperazinyl]-2-isopropylvaleronitrile

TLC(CHCl3: MeOH=9:1) Rf=0.70
MS 421(M+)
H-NMR(CDCL3)
0.81(3H,d,J=7Hz) 1.22(3H,d,J=7Hz)
1.5-1.7(2H,m) 2.15(1H,qq,J=7,7Hz)
2.2-2.5(2H,m) 3.0-3.6(10H,m)
3.89(3H,s) 3.95(3H,s)
6.88(2H,d,J=8Hz) 6.95(2H,d,J=2Hz)
7.04(2H,dd,J=8,2Hz) 7.1-7.2(3H,m)
7.37(2H,dd,J=8,8Hz)

compound 103

5-[4-(4-Fluorobenzoyl)-1-piperidinyl]-2-phenylvaleronitrile

TLC(CHCl3:MeOH=9:1) Rf=0.54
MS 364(M+)
H-NMR(CDCL3)

1.6-1.8(2H,m,) 1.8-1.9(4H,m)
1.9-2.0(2H,m) 2.0-2.2(2H,m)
2.41(2H,t,J=7Hz) 2.9-3.0(2H,m)
3.20(1H,m) 3.88(1H,t,J=7Hz,)
7.1-7.2(2H,m) 7.3-7.4(5H,m,)
7.9-8.0(2H,m)

compound 104

2-(3,4-Dimethoxyphenyl)-5-[4-(4-fluorophenyl)methylene-1-piperidinyl]-2-isopropylvaleronitrile

TLC(CHCl3: MeOH=9:1) Rf=0.73
MS 450(M+)
H-NMR(CDCL3)
0.80(3H,d,J=8Hz) 1.20(3H,d,J=8Hz)
1.5-3.6(15H,m) 3.9-4.0(6H,m)
6.4-6.5(1H,m) 6.8-7.2(7H,m)

compound 105

2-Butyl-2-(3,4-dimethoxyphenyl)-5-[4-(4-fluorobenzoyl)-1-piperidinyl]valeronitrile

TLC(CHCl3:MeOH=9:1)	Rf=0.67
MS	480(M+)
H-NMR(CDCL3)	
0.86(3H,t,J=8Hz)	1.0-3.8(21H,m)
3.88(3H,s)	3.96(3H,s)
6.87(1H,d,J=8Hz)	6.92(1H,s)
6.99(1H,d,J=8Hz)	7.18(2H,dd,J=8,8Hz)
7.92(2H,dd,J=8.6Hz)	

compound 106

5-[4-(4-Fluorobenzoyl)-1-piperidinyl]-2-isopropyl-2-(1-methylpyrrole-2-yl)valeronitrile

TLC(CHCl3: MeOH=9:1)	Rf=0.54
MS	409(M+)
H-NMR(CDCL3)	
1.00(3H,d,J=7Hz)	1.08(3H,d,J=7Hz)
1.4-1.5(1H,m,CH2CCN)	1.5-1.7(1H,m,CH2CCN)
1.7-1.9(4H,m)	1.9-2.1(4H,m)
2.24(1H,hept,J=7Hz)	2.3-2.4(2H,m)
2.8-2.9(2H,m)	3.18(1H,pseud hept.)
3.74(3H,s)	6.00-6.03(1H,m)
6.10-6.14(1H,m)	6.52-6.54(1H,m)
7.09-7.16(1H,m)	7.93-7.98(2H,m)

compound 107

[2-(2-Nitrobenzenesulfonyl)aminoethyl]-4-(4-fluorobenzoyl)piperidine

MS(FAB,m/z)	436(MH+)
NMR	
1.80-2.05(5H,m)	3.04-3.35(6H,m)
3.56-3.65(2H,m)	3.65-3.75(1H,m)
7.90-7.95(2H,m)	7.40(2H,dd,J=8,8Hz)
8.45(1H,bs)	8.02-8.13(4H,m)

compound 108

2-(3,4-Dimethoxyphenyl)-5-[4-(4-fluorobenzoyl)-1-piperidinyl]valeronitrile

MS(m/z)	424(M+)
NMR	
1.8-2.4(8H,m)	2.9-3.7(6H,m)
3.85(3H,s)	3.88(3H,s)
3.8-4.4(2H,m)	6.8-6.9(3H,m)
7.1-7.2(2H,m)	7.9-8.0(2H,m)

compound 109

1-[2-(2-Ethoxycarbonylaminobenzenesulfonyl)aminoethyl]-4-(4-fluorobenzoyl)piperidine

MS(FAB,m/z)	478(MH+)
NMR	
1.12(3H,t,J=8Hz)	1.82-2.10(5H,m)
3.12-3.27(2H,m)	3.65-3.77(4H,m)
4.10(2H,q,J=8Hz)	4.23-4.30(2H,m)
6.16(1H,br)	6.68(1H,dd,J=8,8Hz)
6.89(1H,d,J=8Hz)	7.36(1H,dd,J=8,8Hz)
7.40(2H,dd,J=8,6Hz)	7.59(1H,d,J=8Hz)
8.10(2H,dd,J=8,6Hz)	

compound 110

Methyl 2-[N-methyl-N-2-[2,4(1H,3H)-quinazolinedione-3-yl]-ethylamino]ethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

MS	578(MH+)
NMR	
2.30(3H,s)	2.34(3H,s)
2.38(3H,s)	2.60-2.95(6H,m)
3.83(3H,s)	4.08(2H,t,J=7Hz)
4.04(1H,s)	5.86(1H,s)
6.91(1H,dd,J=8,8Hz)	7.08(1H,dd,J=8,8Hz)
7.23(1H,dd,J=8,8Hz)	7.48(1H,dd,J=8,8Hz)
7.70(1H,d,J=8Hz)	7.85(1H,d,J=8Hz)
8.02(1H,s)	

compound 111

1,3-Bis[4-(4-fluorobenzoylpiperidine-1-yl)propane

NMR	
1.65-2.22(12H,m)	2.25-3.33(12H,m)
7.02(4H,dd,J=8,8Hz)	7.88(4H,dd,J=8,6Hz)

compound 112

2-(3,4-Dimethoxyphenyl)-5-[4-(a-hydroxy-4-fluorobenzyl)-1-piperidinyl]-2-isopropylvaleronitrile

MS	469
NMR	
0.78(3H,dd,J=7Hz)	1.1-1.2(4H,m)
1.16(3H,d,J=7Hz)	1.2-1.4(1H,m)
1.4-1.6(2H,m)	1.6-1.9(4H,m)
2.0-2.1(2H,m)	2.19(2H,pseud t,J=8Hz)
2.6-2.9(2H,m)	3.86(3H,s)
3.87(3H,s)	4.26(1H,d,J=7Hz)
6.8-7.1(5H,m)	7.1-7.3(2H,m)

compound 113

2,2-Diphenyl-5-[4-(4-fluorobenzoyl)-1-piperidinyl]valeronitrile

NMR	
1.9-2.1(4H,m)	3.0-3.1(4H,m)
3.2-3.3(2H,m)	3.7-3.8(1H,m)
7.18(2H,dd,J=8,8Hz)	7.2-7.5(10H,m)
7.92(2H,dd,J=10,8Hz)	

compound 114

2-(3,4-Dimethoxyphenyl)-5-[4-(4-fluorobenzoyl)-1-piperidinyl]-2-octylvaleronitrile

MS	536(M+)
NMR	
0.86(3H,d,J=8Hz)	1.0-3.8(14H,m)
3.88(3H,s)	3.96(3H,s)
6.87(1H,d,J=8,2Hz)	6.92(1H,d,J=2Hz)
6.99(1H,dd,J=8,2Hz)	7.18(2H,dd,J=8,8Hz)
7.90(2H,dd,J=10,8Hz)	

compound 115

4-(4-Fluorobenzoyl)-1-[2-(N-phenylcarbamoylamino)ethyl]piperidine

MS	369(M+)

EXAMPLES

Evaluation of antiarrhythmic activity of the compounds

Example 1

Female Guinea Pigs, weighing 250-350g, were anesthetized with urethane. The lead II ECG was continuously recorded.

Drugs, compound 1 and compound 2, were dissolved in the 2.5% nicol 2.5% ethanol solution, and injected into the femoral vein.

After 30min of drug injection ouabain was infused intravenously through the left femoral vein at a rate of 10ug/kg/min.

The time, ventricular premature contractions (VPC) ventricular fibrillation (VF) and cardiac arrest (CA) appeared on ECG, were measured, and the cumulative ouabain dosage to induce ventricular premature contractions,

ventricular fibrillation and cardiac arrest, respectively, was calculated.

The results are summarized in Table 1.

Example 2

Mongrel dogs of either sex, weighing 8-20 kg, were anesthetized with pentobarbitone sodium, 30mg/kg. The lead II ECG, atrial electrogram from catheter tip electrodes in the right atrium, and blood pressure were continuously recorded. Ouabain 40 ug/kg was injected intravenously and with an additional 10 ug/kg every 20 min until stable ventricular arrhythmias were produced. The severity of arrhythmia was expressed by the arrhythmic ratio i.e. number of ventricular ectopic beats divided by the total heart rate. The arrhythmic ratio was calculated for 60 min after bolus intravenous administration.

The results are summarized in Table 2.

Example 3

Mongrel dogs of either sex, weighing 8-20 kg, were anaesthetized initially with thiopentone sodium. After incubation, 1.0% halothane, vaporized with 100% 02, was administered with volume limited ventilator. Adrenaline was infused through the left femoral vein at the rate of 2.5-5 ug/kg/min. After 3 min of adrenaline infusion, drugs were injected into the right femoral vein. The lead II ECG, atrial electrogram from catheter tip electrodes in the right atrium and blood pressure were continuously recorded. The severity of ectopic beats divided by the total heart rate. The arrhythmic ratio was calculated for 15 min after drug administration.

The results are summarized in Table 3.

Example 4

Three mice were subjected to one group experiment.

Drugs were administered with intraperitoneal injection in three mice 30min before deep chloroform anaesthesia. If less than two mice displayed cardiac arrhythmia or tachycardia, above 200 beats/min, when exposed to deep chloroform anaesthesia, the drug was judged as having an antiarrhythmic effect.

The results are summarized in Table 4.

TABLE 1

Compound #	Dose (mg/kg)	VPC (μ g/kg)	VF (μ g/kg)	CA (μ g/kg)
control		153	221	324
9	1	169	236	294
10	1	166	245	304
11	1	163	256	304
13	1	169	253	299
14	1	144	333	416
16	1	172	217	273
17	1	184	275	380
18	1	203	330	395
20	1	181	366	420
21	1	163	334	393
22	1	178	346	409
23	0.3	142	442	499
24	1	168	250	306
25	1	155	269	326
27	1	163	255	309
28	1	150	291	348
29	1	159	288	344
30	1	145	279	358
31	1	113	271	349
32	1	212	308	374
33	1	152	606	646
34	1	125	556	579
35	1	159	342	413
36	1	149	344	399
37	1	160	298	368
38	1	175	357	427
39	1	254	334	422
40	1	170	321	372
41	1	152	295	357
42	1	225	386	454
43	1	203	372	469
44	3	205	617	656
45	1	147	335	389
46	1	180	347	431
47	1	240	265	351
48	1	212	247	334
49	1	140	311	380
51	1	146	259	344
52	3	205	441	476
53	3	202	398	458
54	1	193	264	350
55	1	175	320	374
56	3	187	254	309
57	1	136	280	346
58	3	174	384	448

TABLE 1 (continued)

Compound #	Dose (mg/kg)	VPC (μg/kg)	VF (μg/kg)	CA (μg/kg)
59	1	203	367	419
60	1	186	534	586
61	1	232	294	356
62	1	186	389	454
63	1	211	322	398
64	1	121	309	365
65	1	146	325	381
66	3	164	264	312
67	3	155	193	245
69	3	185	202	274
70	1	153	373	432
72	1	171	282	363
74	1	182	239	289
75	1	178	257	305
76	1	196	205	274
77	1	179	310	369
78	1	154	279	337
79	1	172	302	358
80	1	200	329	383
81	1	183	267	329
82	1	160	285	339
83	1	176	261	305
84	1	168	277	335
85	1	184	270	318
86	1	162	240	292
87	1	199	260	305
88	1	185	254	318
89	1	204	257	312
90	1	178	228	273
91	1	169	286	338
94	1	178	301	357
95	1	174	264	305
96	1	178	264	312
97	1	134	332	397
98	1	160	318	370
100	1	185	275	355
101	1	161	221	293
102	1	163	246	297
103	1	184	308	351
104	1	168	244	311
106	1	199	312	362

TABLE 2

time after administration (min)	Arrhythmic Ratio Compound # 23 30ug/kg	Compound #75 300ug/kg
0	1.00	1.00
2	1.00	0.80
4	1.00	0.71
6	0.60	0.41
8	0.77	0.19
10	0.50	0.19
12	0.50	0.43
15	0.50	0.43
20	0.00	0.38
30	0.00	0.45
60	0.00	0.45

TABLE 3

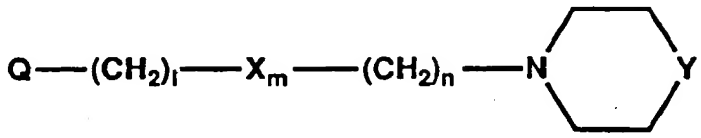
time after administration (min)	Arrhythmic Ratio Compound #23 10ug/kg	Compound #75 300ug/kg
0	1.00	1.00
2	0.80	0.66
4	0.50	0.41
6	0.00	0.18
8	0.00	0.08
10	0.00	0.07
12	0.00	0.07
15	0.00	0.00

TABLE 4

Compund #	minimam effective dose (mg/kg)
107	100
108	50
109	100
110	100
111	100
112	100
113	10
114	25
115	50

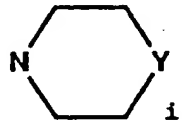
Claims

1. A piperidine derivative of general formula (I) or a pharmaceutically acceptable salt thereof:

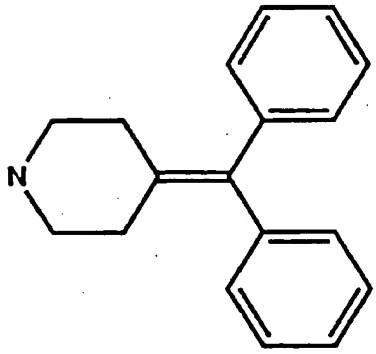


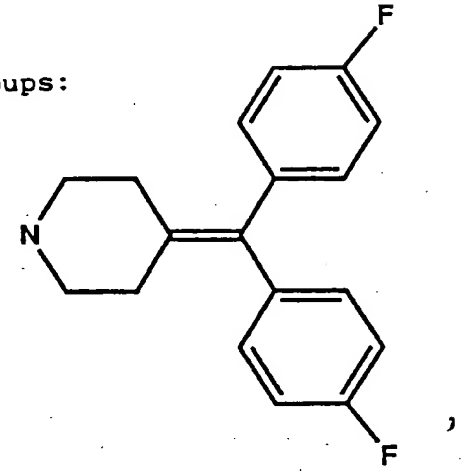
(I)

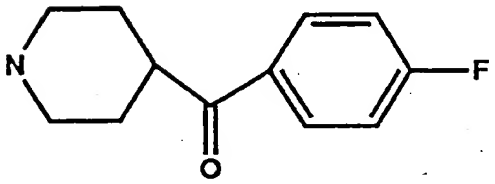
wherein

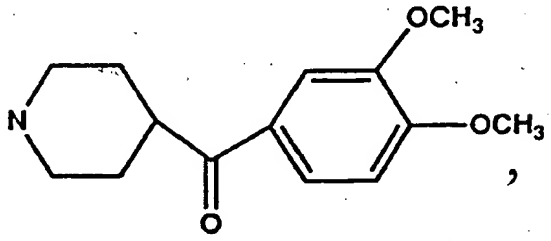


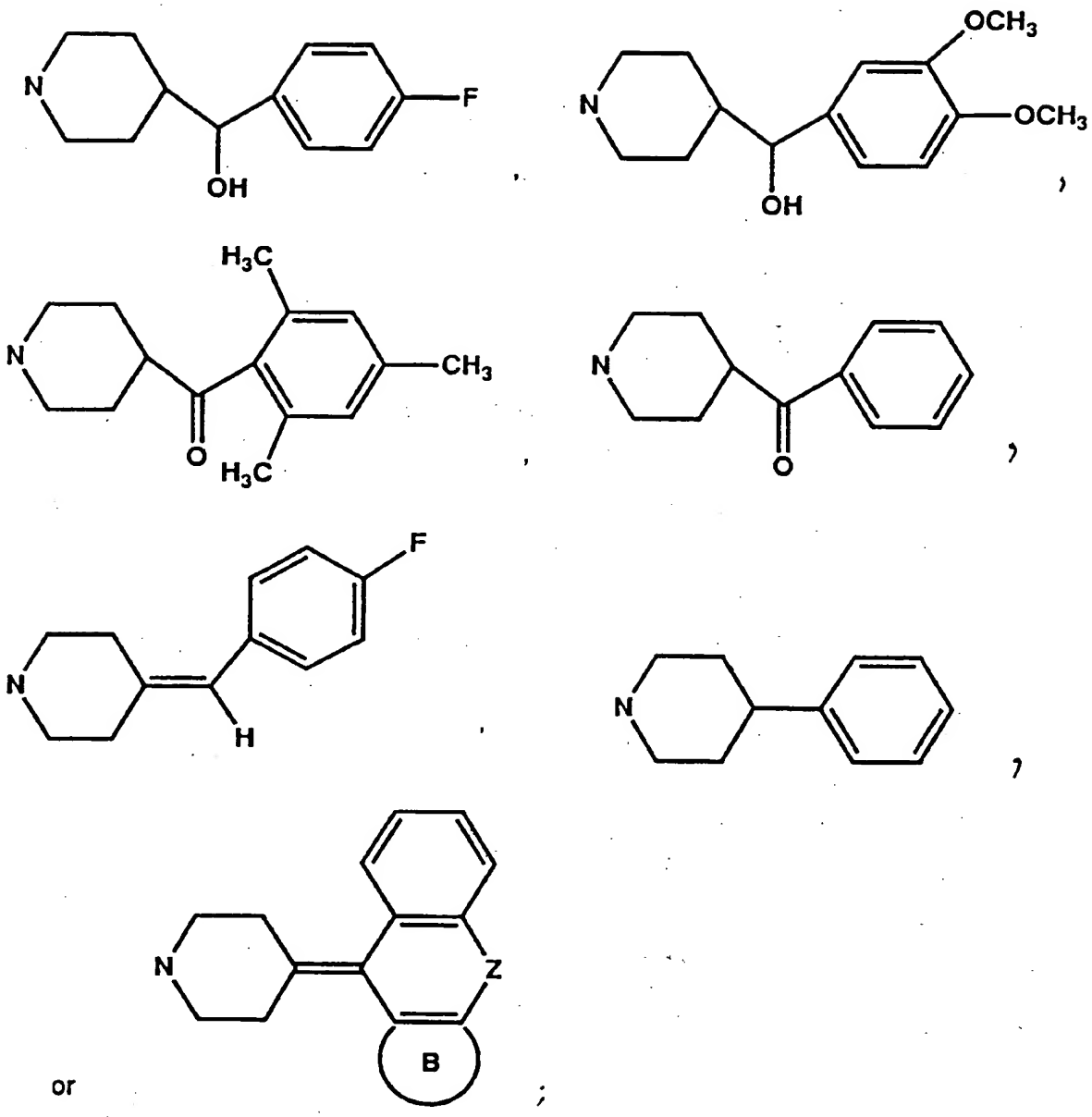
is any of the following groups:







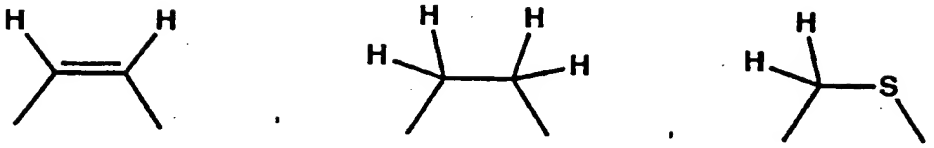


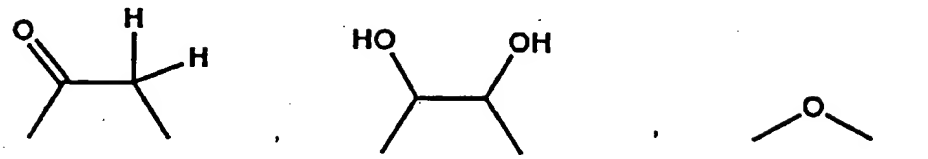


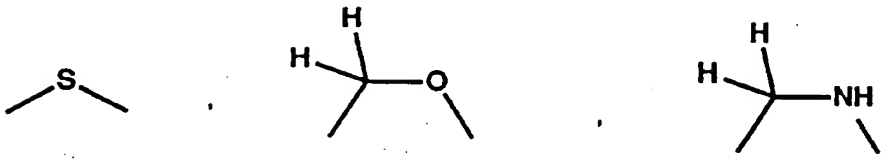
wherein B is a fused aromatic or heterocyclic ring selected from the group consisting of benzene, pyridine and thiophene;

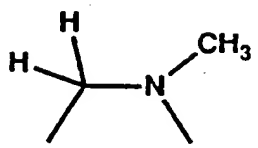
—Z—

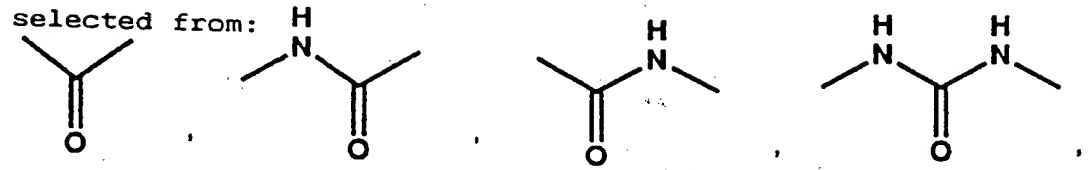
is selected from:

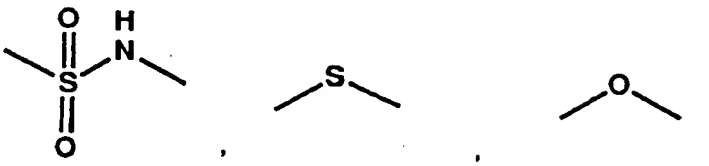


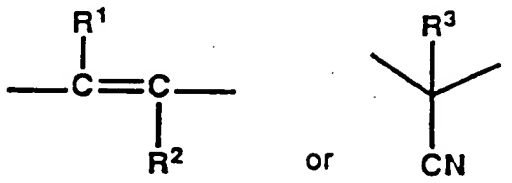




or  ;

X is selected from: 





wherein R^1 and R^2 are the same or different and are independently selected from hydrogen, methyl, ethyl, or propyl; R^3 is hydrogen, alkyl of from 1 to 12 carbon atoms, or aryl of from 6 to 12 carbon atoms;
Q is phenyl, cyclohexyl, piperidinyl, tetrahydropyranyl, pyridyl, pyrrolyl, N-methylpyrrolyl, thienyl, furyl, 1-hexyl, or cyano;
from 1 to 3 hydrogen atoms in Q may be independently substituted by alkyl of from 1 to 3 carbon atoms, perfluoroalkyl of from 1 to 3 carbon atoms, acylamino of from 1 to 6 carbon atoms, perfluoroacylamino of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, alkanesulfonylamino of from 1 to 3 carbon atoms, perfluoroalkanesulfonylamino of from 1 to 3 carbon atoms, acetoxy of from 1 to 3 carbon atoms, aminocarbonyl, aminosulfonyl, fluoro, chloro, cyano, hydroxy, nitro, amino, imidazolylmethyl, cinnamoylamino, p-fluorobenzoyl, cyanomethyl, cyanoethyl, methoxyacetoxy, alkoxycarbonyl of from 1 to 3 carbon atoms:
l is an integer of from 0 to 1;
m is an integer of from 0 to 1;
n is an integer of from 0 to 6.

2. A piperidine derivative or pharmaceutically acceptable salt thereof according to claim 1 for use in the treatment of cardiac arrhythmia.

3. A piperidine derivative according to claim 1 which is any one of compounds 1 to 115 identified herein, or a pharmaceutically acceptable salt thereof.

4. A composition for treating cardiac arrhythmia comprising a mixture of a piperidine derivative or pharmaceutically acceptable salt thereof according to claim 1 and a pharmaceutically acceptable vehicle, diluent, carrier, extender, binder, swelling agent, lubricating or wetting agent, antiseptic, stabilizer, buffer, antioxident, sweetener or flavour.

5. A composition according to claim 4 in unit dosage form.

6. A composition according to claim 5, containing from 0.2 to 500 mg of the piperidine derivative or pharmaceutically acceptable salt thereof.

7. A composition according to any one of claims 4 to 6 in the form of a tablet, capsule, elixir, or a sterile solution or suspension.

8. Use of a piperidine derivative or a pharmaceutically acceptable salt thereof according to claim 1 in the treatment of cardiac arrhythmia.

9. Use of a piperidine derivative or a pharmaceutically acceptable salt thereof according to claim 1 in the preparation of an antiarrhythmic agent.

10. A method of reducing or eliminating cardiac arrhythmia, comprising administering orally or parenterally an effective amount of a piperidine derivative or pharmaceutically acceptable salt thereof according to claim 1.

11. A method according to claim 10, in which the administration is an oral administration of a daily dose of from 0.001 to 2000 mg of the piperidine derivative or pharmaceutically acceptable salt thereof.

12. A method according to claim 10, in which the administration is a parenteral administration of a daily dose of from 0.001 to 1000 mg of the piperidine derivative or pharmaceutically acceptable salt thereof.

13. A method according to claim 10, in which the administration is of a unit dose of from 0.001 to 500 mg of the piperidine derivative or pharmaceutically acceptable salt thereof.